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The primary purpose was to study various aspects of malaria risk assessment, prevention, and treatment. Scope of work included testing malaria vaccines and drugs, and basic work on immunology and mosquito transmission of malaria. Accomplishments included: 1) completed a field test of Pf66 vaccine that showed it to be insufficiently efficacious to warrant further study; 2) began field tests of the recombinant RTSS circumsporozoite vaccine, which had proved 70% efficacious in Phase I; 3) discovered that a subpopulation of trophozoites sequester in the placenta putting both the mother and fetus at increased risk; 4) identified an immune mechanism that appears to explain the unusually high rates of hemolytic anemia encountered in severe malaria in Kenyan children; 5) determined that nearly 40% of infected children did not respond to Fansidar; 6) showed that the primaquine analog Tafenaquine (WR238605) had great promise as a one dose per month prophylaxis; 7) discovered 65 years of admissions records at Kericho that showed no relation between global warming and recent increases in incidence; and 8) used global positioning systems to determine that during the annual dry season *Anopheles gambiae* continues to breed in a few small widely separated springs.

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FOREWORD

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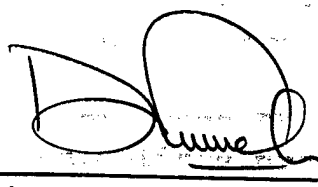

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INTRODUCTION:

The 1995-98 Statement of Work addressed exclusively malaria research, in three areas: immunology and vaccine testing; drug testing; and studies on transmission. All work to be discussed, unless otherwise stated, was conducted in Nyanza Province, in western Kenya, focus of some of the highest rates of malaria transmission in the world. The US Army Medical Research Unit (MRU) maintains a large laboratory at the Kenya Medical Research Institute's (KEMRI) Centre for Vector Research and Control (VRC) at Kisian, in the endemic area, as well as at KEMRI headquarters in Nairobi. Most field sites are within 30 minutes drive from the field station.

Studies on improved means of preventing and treating malaria are of the utmost importance to both Kenya and the US Army. Malaria is the most widespread and debilitating parasitic disease in the world. Falciparum malaria is responsible for as much as 40% of child mortality in some regions of Kenya. The lack of a vaccine, rapidly spreading drug resistance, and the difficulty of effective vector control have also pushed malaria to the top of the Department of Defense's list of priorities for infectious disease research. The high rates of transmission in Kenya and the sophisticated resources of KEMRI have made the collaboration with the MRU especially fruitful. MRU's collaboration with KEMRI has been uninterrupted since the founding of the Institute more than 25 years ago.

Prior work supported by the Cooperative Agreement (CA) included not only malaria but also Rift Valley Fever, leishmaniasis, trypanasomiasis, and enteric infections. The emphasis of earlier work was predominately epidemiology and immunology and has contributed significantly to our understanding of how these diseases are transmitted, how threats can be rapidly assessed, and, in some cases, predicted. The time invested in these earlier studies to characterize large field sites was crucial during the 1995-98 period for providing the raw material for even more sophisticated laboratory and field studies.

SUMMARY OF RESEARCH ACCOMPLISHMENTS

Malaria Vaccine.

During the 1995-98 period evaluation of the Spf66 (Patarroyo) vaccine was concluded. Although it provided some immunogenicity, it did not provide identifiable protection (Masinde GL, et al; Am J Trop Med Hyg. 1998 59:600-5), a result similar to those in Tanzania and Gambia. Trials on a much more promising and less controversial vaccine candidate, RTSS, were begun in 1998. RTS,S is a fusion protein containing a *P. falciparum* circumsporozoite epitope components of hepatitis B antigen. When administered in Phase I trials in the USA and Belgium with proprietary adjuvants manufactured by Smith Kile Beecham, it was not toxic and highly immunogenic. When volunteers were challenged in Phase IIa trials it provided as high as 86% protection against infective inocula. A repetition of Phase I for this highly promising candidate was begun in 20 adult Kenyan volunteers from the village of Kombewa, Nyanza Province in October 1998. This will be followed by Phase II trials during the CA 98-01.

Malaria Immunology

One of the most enduring mysteries about clinical malaria was solved by US and KEMRI personnel during the period of 1995-98 (Science, 1996, 272:1502). It has long been known that pregnant women, especially those with their first child, are highly susceptible to *P. falciparum* infection. They are more likely both to suffer from anemia and to suffer miscarriages. The biological basis of this phenomenon was discovered by us to be parasite sequestration in the placenta. A sub-population of the parasites were shown to bind chondoitin sulfate A adhere to the trophoblastic villi of the placenta, resulting in the accumulation of inflammatory leukocytes in the intravillous spaces and subsequent necrosis. Because women have little experience with this subclass of parasites before they are pregnant, primigravid women are especially at risk; subsequent pregnancies cause decreasing complications. This discovery opens the way to improved therapy for pregnant women, including the possibility of developing specific intervention products, such as drugs and vaccines.

A study correlating infection by falciparum sporozoites with host genetic factors and T cell reactivity to the circumsporozoite protein (SSC #330, WRAIR #416, HSRRB Log A-5669) was also actively pursued. Between 1995 and 1997 a total of 1,784 volunteers were enrolled in this study. During 1998 we enrolled 300 volunteers for follow-up during the long rains and another 100 for follow-up during the short rains. Findings from this ongoing study include: 1) resistance to malaria increases during adolescence, 2) naturally acquired Th2, but not Th1, responses to liver stage antigens correspond to resistance to malaria, 3) immunologic recognition of sequestrin and other malaria antigens is absent in individuals with HLA DR13 alleles, 4) sexual stage antigens are expressed at mRNA level while the parasite is in the human host, suggesting that transmission blocking vaccines may be boosted by infection, and 5) even though expression of VAR gene transcripts by field isolates of parasites has limited heterogeneity, hyperimmune sera rarely inhibits parasite binding to CD36.

Another promising study, begun in May 1998, examines the biological basis of severe anemia in malaria and how its effect compares to that of cerebral malaria. During the last few years anemia has come to be recognized as a pre-eminent cause of disease and death. Among 59 cases of severe anemia studied at Nyanza Provincial Hospital mortality was 22%, compared to 8% among 13 cases of cerebral malaria. Measurement of red cell surface CR1 and CD55 by means of flow cytometry has shown that these complement regulatory proteins are decreased on the surface of cells from patients with severe anemia compared to controls. In addition, red cells from patients with severe anemia are more likely to have associated surface IgG and are more susceptible to in vitro phagocytosis than cells from control volunteers or patients with cerebral malaria. The observed surface changes could make these cells more susceptible to lysis by the action of complement or to phagocytosis by splenic macrophages. Whole blood is now being analyzed for plasma cytokines and *in vitro* cytokine stimulation. Future studies will determine if children at risk of severe malarial anemia are more likely to have the observed red cell surface changes with each bout of infection than controls. No publications have yet resulted from this work.

Malaria Drugs.

The purpose of the MRU antimalarial drug field testing was to conduct first field trials of candidate prophylactic antimalarials that have passed pre-clinical, phase I human pharmacology

and initial human efficacy testing in the USA. Upon COL G. Dennis Shanks' arrival at the end of 1994 to supervise this program, there were four candidate drugs scheduled for testing: azithromycin, atovaquone/ proguanil, halofantrine and WR 238605. In the subsequent four years a disposition has been reached for all four drugs with one being dropped as inadequately efficacious, one licensed in Kenya and pending licensure in the US, one being dropped as potentially toxic and one pending larger scale efficacy trials prior to licensure.

Azithromycin is related to the macrolide antibiotic erythromycin and had demonstrated promise as a possible replacement for daily doxycycline chemoprophylaxis during human challenge trials at WRAIR. Using the Saradidi Rural Health Project in rural Asembo District as a study site, a randomized, double blinded, placebo controlled study was conducted in semi-immune Kenyan adults in 1995 using daily and weekly azithromycin, daily doxycycline and placebo.). The prophylactic efficacy of the groups were: daily azithromycin 83% (95% CI, 68%-91%), weekly azithromycin 64% (95% CI, 50%-75%), daily doxycycline 93% (95% CI 80%-97%). All antibiotic regimens were well tolerated. Both 100 mg doxycycline and 250 mg of azithromycin given daily were effective for malaria prophylaxis. Despite the expense and marginal efficacy of daily azithromycin, a decision was made that this drug was promising enough to try to replicate the Kenyan experience in other areas. Field studies in both Thailand and Indonesia confirmed that the efficacy of daily azithromycin for the prevention of falciparum malaria was sub-optimal (< 90% protection in non-immunes) and further work on azithromycin as an antimalarial has been discontinued.

Atovaquone/ proguanil is a new proguanil combination shown to be very effective for the treatment of acute uncomplicated falciparum malaria due to multiply drug resistant strains from South East Asia. The first chemoprophylactic testing of this new combination was in the rural Lwak field site near Lake Victoria by MRU in 1996. 198 adult volunteers received a treatment course of atovaquone/ proguanil followed by daily drug consisting of high dose (2 tablets) atovaquone/ proguanil, low dose (one tablet) atovaquone/ proguanil or placebo. Of the evaluable subjects (82% of total prophylaxis enrollees), all in the low-dose (54/54) and high-dose (54/54) atovaquone/proguanil groups remained malaria-free during the 10-week prophylaxis period, in contrast to only 48% (26/54) in the placebo group ($P<0.001$). The atovaquone/proguanil treatment regimens were as well tolerated as placebo. Within one year this study had been replicated in Gabonese children, Zambian adults and South African soldiers. The MRU results were confirmed in all three studies and atovaquone/ proguanil has now been registered for treatment and prophylaxis in Kenya and a New Drug Application has already been submitted to the US Food and Drug Administration.

Halofantrine is a US Army antimalarial used to treat acute uncomplicated malaria. It was thought that it might be possible to use halofantrine for malaria prevention. Rare lethal adverse events due to cardiac arrhythmias stopped the planned field testing of halofantrine for prophylaxis. The alternative compound desbutylhalofantrine, which has no cardiac effects, is now undergoing pre-clinical trials.

WR 238605, now called tafenaquine, is a long-acting primaquine analogue that had been shown to prevent malaria when given during human challenge experiments at WRAIR. Another field trial in semi-immune Kenyan adults was done in 1997 in rural Siaya district. Three

different dosage regimens of tafenaquine were tested (three days loading only, loading followed by 250 mg weekly, loading followed by 500 mg weekly) against placebo. Of the evaluable subjects (86% of those randomized, 91% of those starting tafenaquine), volunteers who received 500 mg tafenaquine for only 3 days had a protective efficacy of 74% (95% CI 60-84%) compared to placebo, those receiving 250 mg for 3 days followed by 250 mg weekly had a protective efficacy of 92% (95% CI 82-97%), and those receiving 500 mg for 3 days followed by 500 mg weekly had a protective efficacy of 94% (95% CI 84-98%). Two hemolytic events were noted in volunteers whose G6PD status was in error. Adverse events were reported in a similar number of volunteers in the four treatment groups. Similar studies have since been done in adults in Ghana and Thailand. Further testing of the short course three-day regimen of tafenaquine is planned for 1999 in the Kericho Tea Estates where the length of the transmission season is limited by cold temperatures.

There is very little known about the emergence and distribution of resistant strains of malaria in East Africa. The establishment of a systematic in vitro testing program is urgent; such a facility was begun in 1998 and should become fully operational during the 1999-01 CA. The primary treatment for uncomplicated acute falciparum malaria in Kenya is sulfadoxine/ pyrimethamine. Working with Dr Bernard Ogutu, of KEMRI, at Kenyatta National Hospital, a quarter of all pediatric malaria patients was shown to fail to cure with standard doses of sulfadoxine/ pyrimethamine. Drug resistance particularly to new study drugs has also been monitored during all MRU drug field trials. Comparing the three identically designed field trials during 1995-97 in regard to time to reappearance of falciparum malaria following treatment, it was found that the survival curves of aparasitemic volunteers were very reproducible from year to year. This observation confirms the validity of using semi-immune adults in holoendemic areas as an initial test population for new antimalarial prophylactic drugs.

Malaria Transmission Studies.

Although malaria transmission in the vicinity of Kisian is intense - as high as 150 inoculations per person annually - it is also seasonal. The highest risk, as determined in earlier studies by us, is during the March-July rainy season, when the populations of *Anopheles gambiae* and *An. arabiensis* are highest. These two related species virtually disappear during the dry seasons. Research conducted by Dr. R. Dunton (MRU) and Dr. A. Githeko (KEMRI) was aimed at discovering how these vectors survived the dry season and whether they might be susceptible to attack then. This study, which is not yet completed, uses state-of-the-art global positioning (GPS) technology to precisely map the seasonal changes in vector breeding places. They have established that in fact the two species do not disappear but continue to breed at much reduced numbers in widely separated seepages. Current efforts are to determine if they are still able to maintain the transmission cycle among people living proximal to these atypical breeding sites.

Most areas of malaria transmission in Kenya are not so intense as at Nyanza. There has been increasing concern that the amount of malaria in the highlands ($\geq$ 1,500m asl) has increased recently. Under the leadership of Dr. Shanks we have established a new field site in the tea plantations surrounding Kericho (>2,100m asl). Using retrospective and prospective data from the Brooke Bond Kenya Ltd. tea company, we have established that indeed clinical cases of

malaria have increased there significantly during 1993-1998, but were able to eliminate climate change as the primary factor, suggesting that parasite resistance to chloroquine may be involved.

Emerging Disease and Miscellaneous Surveillance.

A randomized, double-blinded study comparing 1 gram of azithromycin and 3 days of ciprofloxacin (500 mg twice a day) for the treatment of shigella dysentery was conducted in western Kenya during July 96 – June 97. No significant differences were observed between treatment groups for the resolution of dysentery, fever or fluid support. *S dysenteriae* type 1 isolates were resistant to the commonly prescribed drugs tetracycline and ampicillin-trimethoprim / sulfamethoxazole-erythromycin. In a preliminary study of bacterial agents and antimicrobial resistance patterns found in acute diarrheal disease in 317 children living in Kibera, Kenya, April – June 1997,67% of the isolates were pathogenic E. coli; 23% were shigella; high levels of resistance to commonly prescribed antibiotics were observed. In an enteric outbreak among Rwandan refugees in Tanzania, 1996, 25% of specimens were cultured for shigella. *S. dysenteriae* type I was isolated from 20 specimens; all were resistant to nalidixic acid.

A Rift Valley Fever epidemic occurred during 1997-8. Working with international, foreign national, and United States medical organizations, such as the World Health Organization - Geneva, Kenya Ministry of Health, foreign nongovernmental agencies (NGO's), and the US Centers for Disease Control and Prevention (CDC) during the outbreak, we conducted a RVF vaccination program under IND conditions for 27 persons. This program insured the safety of laboratory personnel so that specimens could be analyzed quickly in Kenya without the need to send them to the US or South Africa. Investigated the hospitalizations and deaths of RVF patients in Kajiado District. Conducted an epidemiological investigation to determine to the attack rates and mortality rates in a human population.

We lent our expertise to the investigation of a number of other outbreaks during 1995-98.
1) Eleven cases of jaundice and fever with high mortality rate in Muguma during 1997 were thought to be hepatitis B by local health officials. The epidemiology of the cases were not consistent with infectious hepatitis and repeat testing of sera did not confirm hepatitis A or B; most likely a toxin, but limited time and money did not permit a complete investigation.
2) Highland malaria in After heavy rains at West Pokot District in 1997, the number of malaria cases increased greatly in areas where the rate was usually low. Mortality rates were reported to be high. Because this occurred in an area where yellow fever transmission was possible, we investigated the possibility that some of these cases may be due to agents other than malaria. We obtained approx. 60 serum samples from patients in a mission hospital, a rural health clinic, and two district hospitals; there was no serological evidence for yellow fever transmission.
3) Evaluated a patient that had been clinically diagnosed as VHF by the International Red Cross VHF at Kakuma, Kenya in 1997. We helped establish isolation and barrier nursing care. Using IFA testing of the sera, determined that IgM to CCHF, Ebola (Sudan), RVF, Marburg, Lassa and yellow fever were negative.
4) Diarrheal outbreak with deaths, Elangata Enterit. A missionary clinic serving 4-5,000 Maasai at Narok District reported a diarrheal outbreak in May 1998 with several deaths. *Vibrio*

cholerae was isolated from fecal samples for the first time in this area. The organisms were sensitive to tetracycline; medical personnel began using tetracycline and no further deaths occurred.

Training.

An important component of the CA has been in training Kenyans, Americans, and others in the methods of advanced research. Co-sponsored with Dr. Waiyaki the 1st National Workshop on Antimicrobial Drug Susceptibility, Surveillance, and Monitoring in February 1997; 35 Kenyan healthcare workers from the government, academia, private industry, research, and nongovernmental agencies met to create a coordinated approach to antimicrobial monitoring in Kenya. In addition we co-sponsored a workshop for laboratory technicians to standardized data collection. Funding for these activities was provided by the WHO. A list of personnel trained through the CA during 1995-98 is at Appendix A.

CONCLUSIONS

Perhaps the most notable scientific accomplishment during the term of the CA was the discovery of the mechanism by which *P. falciparum* sequesters in the placenta. This opens promising avenues for future research that may lead to improved vaccines and drugs. Several other potentially important projects were begun during the 1995-98 CA:

- the first field trials of RTS,S at a hyperendemic focus
- establishment of a highland malaria site with extraordinary background data
- determination of the surprisingly long efficacy of the primaquine analog, tafenaquine
- the first systematic data linking dry season habitat of *A. gambiae* with malaria transmission

Experience during this CA period strongly suggests not only completing the above projects but initiating several new activities:

- a vigorous in vitro program of surveillance for malaria drug resistance
- research on HIV interaction with malaria in western Kenya
- increased efforts in identifying emerging infectious diseases

The collaboration between KEMRI and MRU continues to be a highly productive one of mutual benefit.

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APPENDIX 1
Three-Year Contract Personnel*

	Grade	Payroll No.	Employee Name	DESIGNATION
1	MR-10	80057	Fred Kiddy Onyango	Senior Lab Technologist
2	MR-10	80044	David Kiplangat Chumo	Senior Lab Technologist
3	MR-10	80068	Joseph Koros	Senior Lab Technologist
4	MR-9	80079	Joyce Macharia	Personnal Secretay I
5	MR-9	80113	Malachi Opollo	Laboratory Technologist I
6	MR-9	80183	Theresa a. Wesonga	Assistant Research Officer
7	MR-9	80182	Zakayo Kadenge	Accountant II
8	MR-9	80229	Margaret W. Muturi	Research Officer
9	MR-9	80234	Bindi A. Gadhi	Assistant Research Officer
10	MR-9	80231	Raphael Pundo Omondi	Computer Programmer I
11	MR-8	80080	Daniel Waema	Supplies Officer III
12	MR-8	80134	Lucy Lodenyi	computer Programmer II
13	MR-8	80071	Charles Asiago	Laboratory Technician I
14	MR-7	80066	Josphat Mwangi Kabui	Laboratory Technician II
15	MR-7	80164	Michael Ouma Opiyo	Laboratory Technologist III
16	MR-7	80233	Joseph Ouya Osoga	Laboratory Technologist III
17	MR-7	80232	Gordon M. Hongo	Laboratory Technologist III
18	MR-7	80039	John Kamanza	Laboratory Technician II
19	MR-7	80063	Christopher Oyaro (onger)	Laboratory Technician II
20	MR-7	80069	Michael Ouko	Laboratory Technician II
21	MR-6	80147	Charles Okundo Okelo	Laboratory Technician III
22	MR-6	80053	Ramadhan Mutalib	Laboratory Technician III
23	MR-6	80035	Agnes Nganga	Computer Operator II
24	MR-5	80049	Nerry Oluoch Ndiege	Junior Laboratory Tech.
25	MR-5	80166	Cathrine Wigwa	Computer operator III
26	MR-5	30029	James Gitonga	Computer Operator III
27	MR-5	80206	John G. Kamau	Driver Grade I
28	MR-5	80230	Valerie A . Oundo	Junior Laboratory Tech.
29	MR-5	80047	Dismas Achango	Junior Laboratory Tech.
30	MR-5	80074	Jecinta Wanjiru	senior Auxilliary Staff
31	MR-5	80042	Samwel Odour Wangowe	Junior Laboratory Tech.
32	MR-4	80045	Joram Osumo	senior Auxilliary Staff
33	MR-4	80034	Samwel K. Ligonzo	senior Auxilliary Staff
34	MR-4	80056	Alex Masinya	senior Auxilliary Staff
35	MR-4	80061	Philistus Oigo Ogilo	senior Auxilliary Staff
36	MR-4	80050	Consolata Onyango	senior Auxilliary Staff
37	MR-4	80167	David L. Madahana	Driver Grade II
38	MR-4	80181	George Nyawade	Driver Grade II
39	MR-4	80168	Abdi Ayub	Driver Grade II
40	MR-3	80054	Silas Ongonga Onguka	Auxilliary Staff I
41	MR-3		Edwin C. Mbwabi	Auxilliary Staff I
42	MR-2	80165	Raphael onyango	Auxilliary Staff II
43	MR-9		Melanie Atieno Onyango	Assistant Research Officer
44	MR-9		Joram Ogola Siagla	Assistant Research Officer
45	MR-2		Maurice Odongo Otieno	Driver Grade III

*about 100 shorter term employees not shown

APPENDIX 2

Personnel Trained at United States Army Medical Research Unit-Kenya

Name	Nationality	Affiliation	Degree	Area	Completed
Mebrahtu, Yemane	Kenya	Nairobi University	PhD, M.Sc	Leish	June-92
Njunge, Luna	Kenya	Kenyatta University	M.S.	Malaria	Jul-93
Ofulla, Ayub	Kenya	Kenyatta Univeristy	PhD, M.Sc	Malaria	Jun-94
Alwi, Shatri	Kenya	Kenyatta University	PhD.	Leish	May-95
Ngumbi, Phillip	Kenya	Nairobi University	PhD, M.Sc	Leish	Jun-95
Angile, Chris	Kenya	Nairobi University	Ph.D.	Leish	Sep-95
Iversen, Elsa	Denmark	University Copenhagen	M.D.	Enteric	Feb-96
Christensen, Melin	Netherlands	Leiden University	M.D.	Malaria	Jun-96
Andresen, Renee	Netherlands	Leiden University	M.D.	Malaria	Jun-96
Kariuki, Michael	Kenya	Nairobi University	M.Sc	Malaria	Jun-96
Malakoti, Mark	Navy	USUHS	MPH	Enteric	Jun-96
Taylor, Kathy	US	ILRI	PhD	African Tryp	Jul-96
Schmit, Margot	Netherlands	University Amsterdam	M.D.	Enteric	Jul-96
Tiemessen, M	Netherlands	University Amsterdam	M.D.	Enteric	Jul-96
Ohas, Eunita	Kenya	Kenyatta University	M.Sc.	Malaria	Aug-96
Masinde, Godfried	Kenya	Tulane University	Ph.D.	Malaria	Sep-96
Nyakeriga, Alice	Kenya	Kenyatta Univeristy	M.Sc.	Malaria	Sep-96
Van Doom, Olga	Netherlands	Univeristy Amsterdam	M.D.	Enteric	Oct-96
Van Eljk, Everline	Netherlands	University Amsterdam	M.D.	Enteric	Oct-96
Muturie, Margaret	Kenya	Kenyatta Univeristy	M.Sc	Malaria	Nov-96
Fried, Michal	Israel	NRC	PhD	Malaria	96-98
Kurtis, Jonathan	US	NRC	PhD	Malaria	96-98
Ngure, Peter	Kenya	Moi Univeristy	M.Sc.	Malaria	1997
Ngure, Veronica	Kenya	Moi Univeristy	M.Sc.	Malaria	1997
Ogola, Bilha	Kenya	Moi University	M.Sc.	Malaria	1997
Siangla, Joram	Kenya	Maseno Univeristy	M.Sc.	Malaria	1997
Obado, Michael	Kenya	Kenyatta Univeristy	M.Sc	Malaria	1997
Odhiambo, Rose	Kenya	Egerton University	Ph.D; M.Sc.	Malaria	1997
Honnas, Arne	Norway	University Norway	M.D.	Enteric/meningi	1997
Peta Petersen	Netherlands	St. Mary's Hospital	M.D.	Statistics	June-97
Dianne Olsen	Netherlands	St. Elizabeth Univ	M.D.	Statistics	June-97
Van Gee, Winfred	Netherlands	St. Elizabeth Univ	M.D.	Statistics	June-97
Caaca, Abrahams	Kenya	St. Mary's Hospital	M.D.	Statistics	June-97
Lars Petersen	Norway	St. Mary's Hospital	M.D.	Enteric	June-97
Ogutu, Ragama	Kenya	Kenyatta National Hosp.	MD	MS Paed.	Sep-98